IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Lindberg, et al.
Serial No.	:	09/419,456
Filed	:	October 15, 1999
For	:	New Compounds
Examiner	:	
Group Art Unit	:	

Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION OF TOMMY ANDERSSON
(Under 37 C.F.R. § 1.132)

Sir:

I, Tommy Andersson, Ph.D., declare as follows:

I am a citizen of SWEDEN. I graduated in 1991 from the University of Gothenburg with a doctorate in Clinical Pharmacology.

AstraZeneca is the parent company of Astra Aktiebolag. The assignee of the referenced application is Astra Aktiebolag. AstraZeneca LP, U.S.A. has employed me from 1998 to the present as Director, Clinical Pharmacology. From 1978 to 1998, I was employed in various positions at Astra Hässle AB, which is also presently part of the AstraZeneca organization. I have read and understood the referenced patent application and I am familiar with the invention described and claimed therein. My curriculum vitae is enclosed (Exhibit A).

Set forth below is a summary of a clinical study performed by Astra Hässle AB on the pharmaceutical formulations of omeprazole having the chemical name, 5-methoxy-2-(((4-methoxy-3, 5-dimethyl-2-pyridiny)methyl) sulfinyl)-1H-benzimidazole, and its (-) enantiomer for intravenous administration. As used herein, omeprazole refers to the racemate and, for ease of discussion in this Declaration, the (+)- and (-)-enantiomers of omeprazole are designated (+)-omeprazole and (-)-omeprazole, respectively.

The study concerns a clinical comparison of the pharmacokinetics of the (-)-omeprazole with omeprazole racemate when each compound is administered intravenously as the sodium salt to

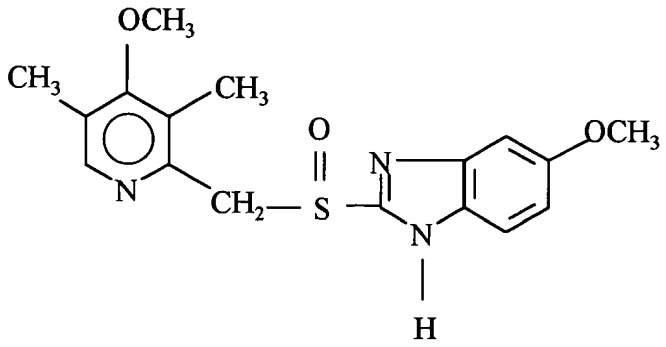
"rapid" and "slow" metabolizers. The sodium salt of the (-)-enantiomer of omeprazole was prepared in a solid state form and formulated into a sterile solution. As a reference, a prepared sterile sodium salt solution of omeprazole for intravenous administration was used.

The results of the study demonstrate that the (-)-enantiomer of omeprazole, administered intravenously as the sodium salt, unexpectedly has a different and more advantageous pharmacokinetic profile in terms of plasma concentrations and interindividual variation than omeprazole racemate, also administered intravenously as the sodium salt. In my opinion, the findings of this study are contrary to the reported conclusions, and the inferences to be drawn therefrom, regarding the pharmacokinetic profile of the enantiomers of omeprazole as published by Cairns, A. et al. "Enantioselective high-performance liquid chromatographic determination of omeprazole in human plasma", Journal of Chromatography B, 666 (1995) 323-328.

It is my understanding that the later publication date of the Cairns et al. article disqualifies that article as prior art. Nevertheless, the publication is representative of the state of the art at the time the invention of the referenced patent application was made. Specifically, Cairns et al. measured the concentrations of (+)-omeprazole and (-)-omeprazole after the intravenous administration of a 20 mg omeprazole dose. Cairns et al. reported that, when a racemic dose of omeprazole is administered intravenously, the concentration of (+)-omeprazole and (-)-omeprazole were essentially equal in the plasma samples that were assayed. Thus, at the time the invention was made, the person of ordinary skill in the art would have expected the pharmacokinetic profile of omeprazole racemate and of each enantiomer to be essentially the same.

Chemical Background

Omeprazole is a racemic mixture (racemate). This is due to the chirality of the sulfoxide moiety in the omeprazole molecule of the following formula



Omeprazole

The (-)-enantiomer of omeprazole and the (+)-enantiomer of omeprazole are simply designated (-)-omeprazole and (+)-omeprazole, respectively.

As described in the referenced U.S. Patent Application Serial No. 09/419,456, the alkaline salts of each of the single enantiomeric forms of omeprazole were obtained in solid state form which

made it possible to further purify the salts by recrystallization attaining both high chemical and optical purity. The solid state form also made it possible to formulate an alkaline salt of the (-)-enantiomer of omeprazole into a stable reproducibly defined dosage form for parenteral administration.

Biological Background

Omeprazole, which is marketed in the U.S.A. as Prilosec®, is a proton pump (H^+/K^+- ATPase) inhibitor which has been used for several years in the treatment of gastric acid-related diseases with good clinical results. A safety assessment, based on more that 300 million prescriptions worldwide, indicates that omeprazole is a safe drug with no reports of dose-dependent side effects. Omeprazole is available for oral administration in the form of an enteric coated formulation. It is also available for parenteral administration in a dosage form based on the sodium salt of omeprazole.

It is a wish that a new pharmaceutically active compound, such as an alkaline salt of the (-)-enantiomer of omeprazole, should be available both for oral and parenteral administration.

"Slow" and "Rapid" metabolizers

It is known that some individuals (about 3% among Caucasians and about 15% among Asians) exhibit higher (5- to 10-fold) than average plasma concentration versus time curves (AUC) of drug. The metabolic capacity of this minority of individuals, who are classified as slow or poor metabolizers (as opposed to the majority who are classified as rapid/extensive or "normal" metabolizers), is genetically determined. It has been found that the reason for the slow metabolism of omeprazole is a lack of cytochrome P450(CYP)2C19 (hereinafter "CYP2C19"). Thus, while rapid metabolizers express CYP2C19, the slow metabolizers do not. Omeprazole is mainly metabolized by the polymorphically expressed enzyme CYP2C19. This results in a several fold difference in plasma levels of omeprazole between those who express an active form of this enzyme and those who do not. And this difference leads to a certain degree of interindividual variation in plasma levels within the total population during treatment with omeprazole.

Study

A comparative study on 40 mg (-)-omeprazole and 40 mg omeprazole with regard to pharmacokinetics after intravenous administration of the sodium salt of (-)-omeprazole and the sodium salt of omeprazole, respectively, after single and repeated doses in healthy male subjects.

The objective of this study was to compare the pharmacokinetics of (-)-omeprazole and omeprazole racemate following single and repeated intravenous administration of daily 40 mg doses of each compound, as the sodium salts, to rapid and slow metabolizers.

An open, randomized, two-way crossover study was conducted consisting of two treatment periods, each with a duration of 5 days and separated by a washout period of 2 weeks. The pharmacokinetics (plasma levels) of the compounds were studied in all subjects on day 1 and day 5 of each period.

Thirteen rapid metabolizers and two slow metabolizers completed the study. The subjects were healthy males varying from 21 to 40 years of age.

The sodium salts of (-)-omeprazole (0.2 mg/mL) and omeprazole racemate (0.4 mg/mL) were administered intravenously as 200 mL and 100 mL, respectively (corresponding to a dose of 40 mg) over approximately 30 minutes.

Summary of results

Mean plasma levels of (-)-omeprazole and omeprazole racemate after single and repeated intravenous dosing of 40 mg of the sodium salt of each compound to rapid metabolizers (13 subjects) are presented in Figure 1. Plasma levels of (-)-omeprazole and omeprazole racemate after single (Day 1) and repeated (Day 5) intravenous dosing of 40 mg of the sodium salt of each compound to two slow metabolizers (named Subject No. 3 and Subject No. 16) are presented in Figures 2 and 3, respectively.

In rapid metabolizers, the geometric mean AUC after both single and repeated intravenous doses of the sodium salt of (-)-omeprazole was more than 40% higher than that after administration of the sodium salt of omeprazole racemate (Table). The higher AUC is the result of lower plasma clearance of the (-)-omeprazole as compared to omeprazole racemate. The reverse relationship is seen in slow metabolizers in that the AUC of (-)-omeprazole was lower than that of omeprazole racemate. As a consequence of these relationships, the AUC of (-)-omeprazole after a single intravenous dose was found to be 2.5-2.9 times greater in slow metabolizers than in rapid metabolizers, while with omeprazole racemate, the difference was greater (4.6-5.0 times). Corresponding differences after repeated dosing were less, approximately 1.5-fold and 3-fold, for (-)-omeprazole and omeprazole racemate, respectively. In addition, there were no differences regarding the volume of distribution for the two compounds.

Table

Geometric means and 95% confidence intervals of area under the plasma concentration-time curve (AUC), plasma half-life (t1/2) and plasma clearance (CL) and the ratio of geometric means following single (Day 1) and repeated (Day 5) intravenous dosing with 40 mg of the sodium salts of (-)-omeprazole and omeprazole racemate to thirteen healthy male rapid metabolizers and corresponding individual values for two healthy male slow metabolizers.

	AUC (μmol*h/L)	$t_{1/2}$ (h)	CL (L/h)
Day 1			
Rapid metabolizers (n=13)			
(-)-omeprazole (A)	7.8 (6.6-9.2)	1.0 (0.8-1.1)	14.9 (12.6-17.5)
Omeprazole racemate (B)	5.4 (4.6-6.4)	0.8 (0.7-0.9)	21.3 (18.1-25.0)
A/B	1.4 (1.3-1.6)	1.3 (1.2-1.3)	0.7 (0.6-0.8)
Slow metabolizers (n=2)			
Subject No. 3			
(-)-omeprazole (C)	22.6	1.9	5.1
Omeprazole racemate (D)	26.9	2.6	4.3
C/A	2.9	1.9	0.3
D/B	5.0	3.3	0.2
Subject No. 16			
(-)-omeprazole (E)	19.7	2.1	5.9
Omeprazole racemate (F)	25.0	2.7	4.6
E/A	2.5	2.1	0.4
F/B	4.6	3.4	0.2
Day 5			
Rapid metabolizers (n=13)			
(-)-omeprazole (A)	14.2 (12.2-16.7)	1.4 (1.2-1.5)	8.1 (6.9-9.5)
Omeprazole racemate (B)	9.9 (8.5-11.7)	1.1 (1.0-1.2)	11.6 (9.9-13.7)
A/B	1.4 (1.3-1.6)	1.2 (1.2-1.3)	0.7 (0.6-0.8)
Slow metabolizers (n=2)			
Subject No. 3			
(-)-omeprazole (C)	23.2	1.9	5.0
Omeprazole racemate (D)	31.8	2.5	3.6
C/A	1.6	1.4	0.6
D/B	3.2	2.3	0.3
Subject No. 16			
(-)-omeprazole (E)	20.8	2.2	5.6
Omeprazole racemate (F)	27.3	2.8	4.2
E/A	1.5	1.6	0.7
F/B	2.8	2.5	0.4

Thus, (-)-omeprazole gives a smaller ratio in AUC between slow and rapid metabolizers compared to omeprazole racemate after intravenous administration of the sodium salts, which demonstrates that (-)-omeprazole is less dependent on CYP2C19 for its metabolism than is omeprazole racemate.

Clinical relevance of the results

I. A larger fraction of patients will have optimal plasma concentrations after administration of the sodium salt of (-)-omeprazole.

As a consequence of the less pronounced difference in AUC between slow and rapid metabolizers, the interindividual variation in AUC of (-)-omeprazole is less than that of omeprazole racemate. This may potentially result in a larger fraction of patients attaining plasma concentrations that would be optimal with respect to the desired gastric acid anti-secretory effect in the clinical situation.

II. Higher AUC giving better overall clinical effect after administration of the sodium salt of (-)-omeprazole.

It was observed that the AUC of (-)-omeprazole in rapid metabolizers was more than 40% higher than of omeprazole racemate after both single and repeated intravenous dosing. Therefore, the anti-secretory effect, which has previously been demonstrated to be directly correlated to the AUC irrespective of compound, can be expected to be higher for (-)-omeprazole than for omeprazole racemate following intravenous administration of identical doses. This, in turn, may be expected to give a clinical advantage for (-)-omeprazole, since the number of patients healed from acid-related diseases is expected to be higher.

Conclusions

The clinical study outlined above demonstrates that the sodium salt of (-)-omeprazole has the following unexpected pharmacokinetic advantages over the sodium salt of omeprazole racemate when administered intravenously:

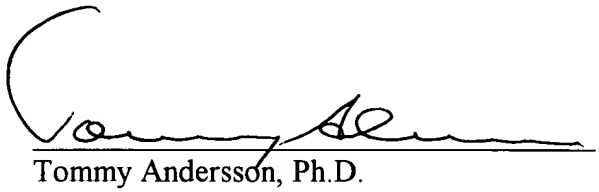
- Less interindividual variation in plasma levels (AUC) between rapid and slow metabolizers provides for a larger fraction of patients with optimal plasma concentrations

- Higher average AUC, which is known to result in a more pronounced inhibitory effect on gastric acid secretion and therefore is expected to result in a better overall clinical effect

Thus, the parenteral formulations comprising the sodium salt of (-)-omeprazole can provide an improved, alternative pharmaceutical formulation for parenteral administration in the treatment of gastric acid-related diseases.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 11/11/99



Tommy Andersson, Ph.D.

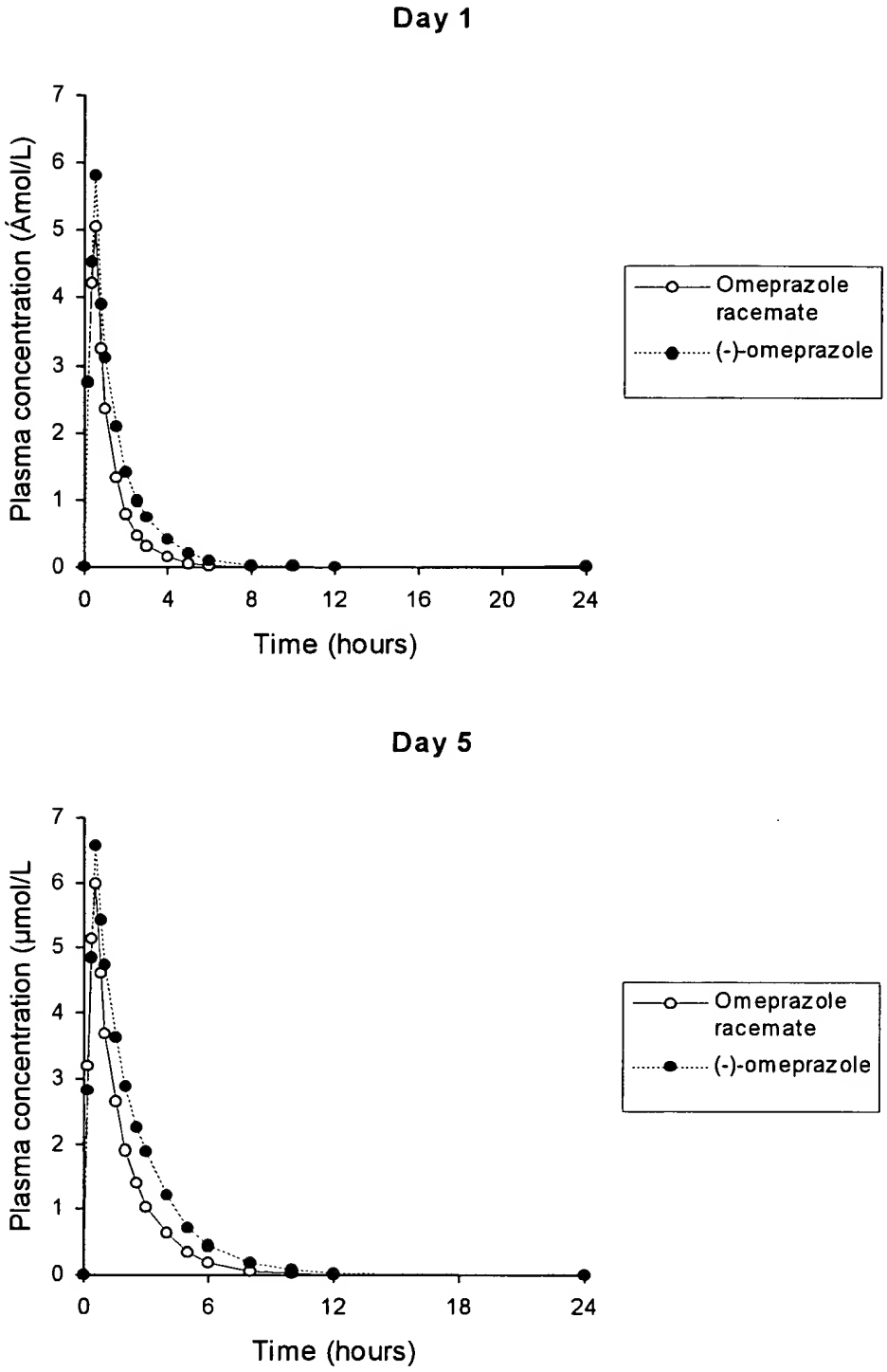


Figure 1. *Mean plasma levels of (-)-omeprazole and omeprazole racemate after single (Day 1) and repeated (Day5) intravenous administration of the sodium salts of daily doses of 40 mg to rapid metabolizers (n=13).*

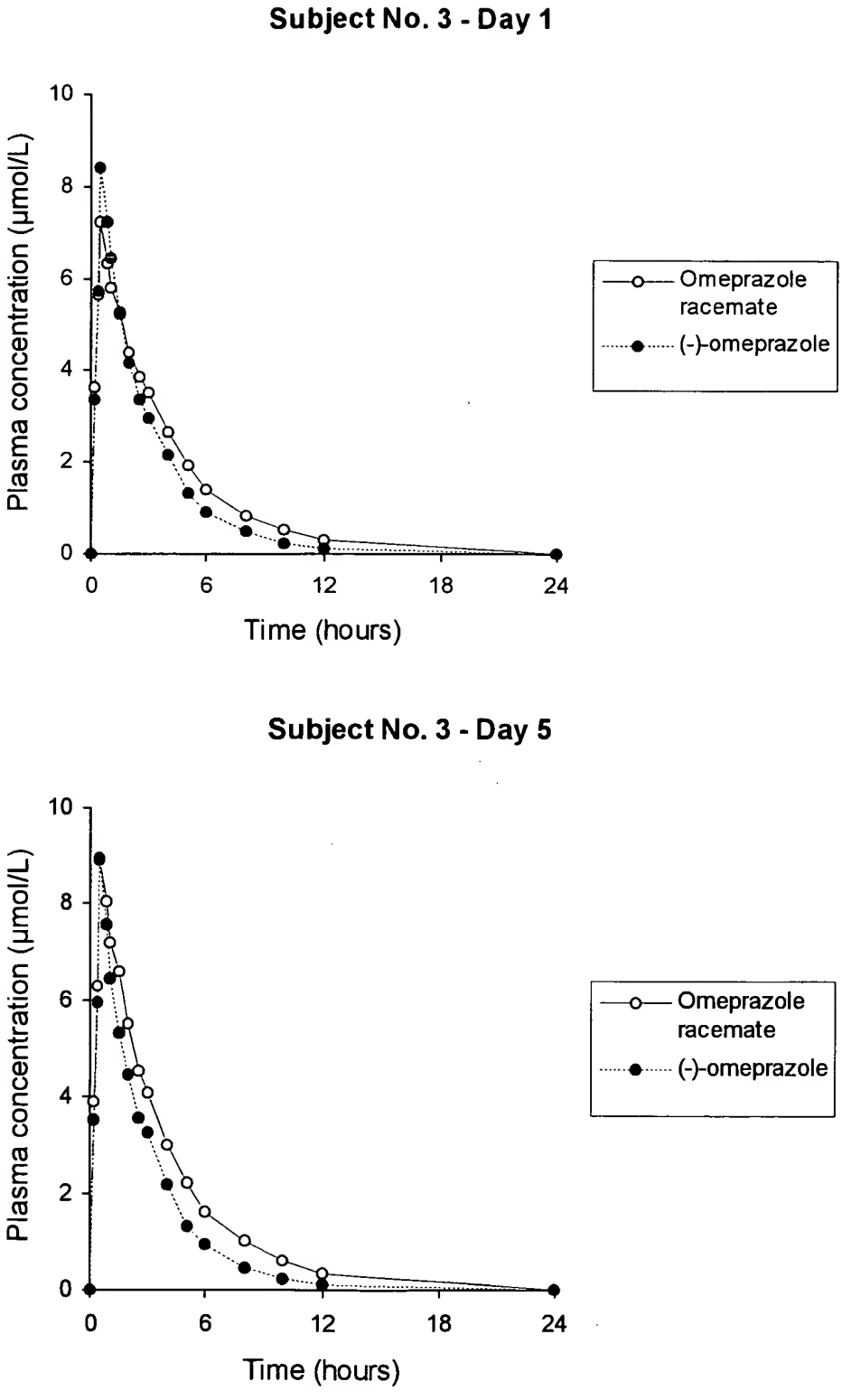


Figure 2. *Plasma levels of (-)-omeprazole and omeprazole racemate after single (Day 1) and repeated (Day5) intravenous administration of the sodium salts of daily doses of 40 mg to a slow metabolizer (Subject No. 3).*

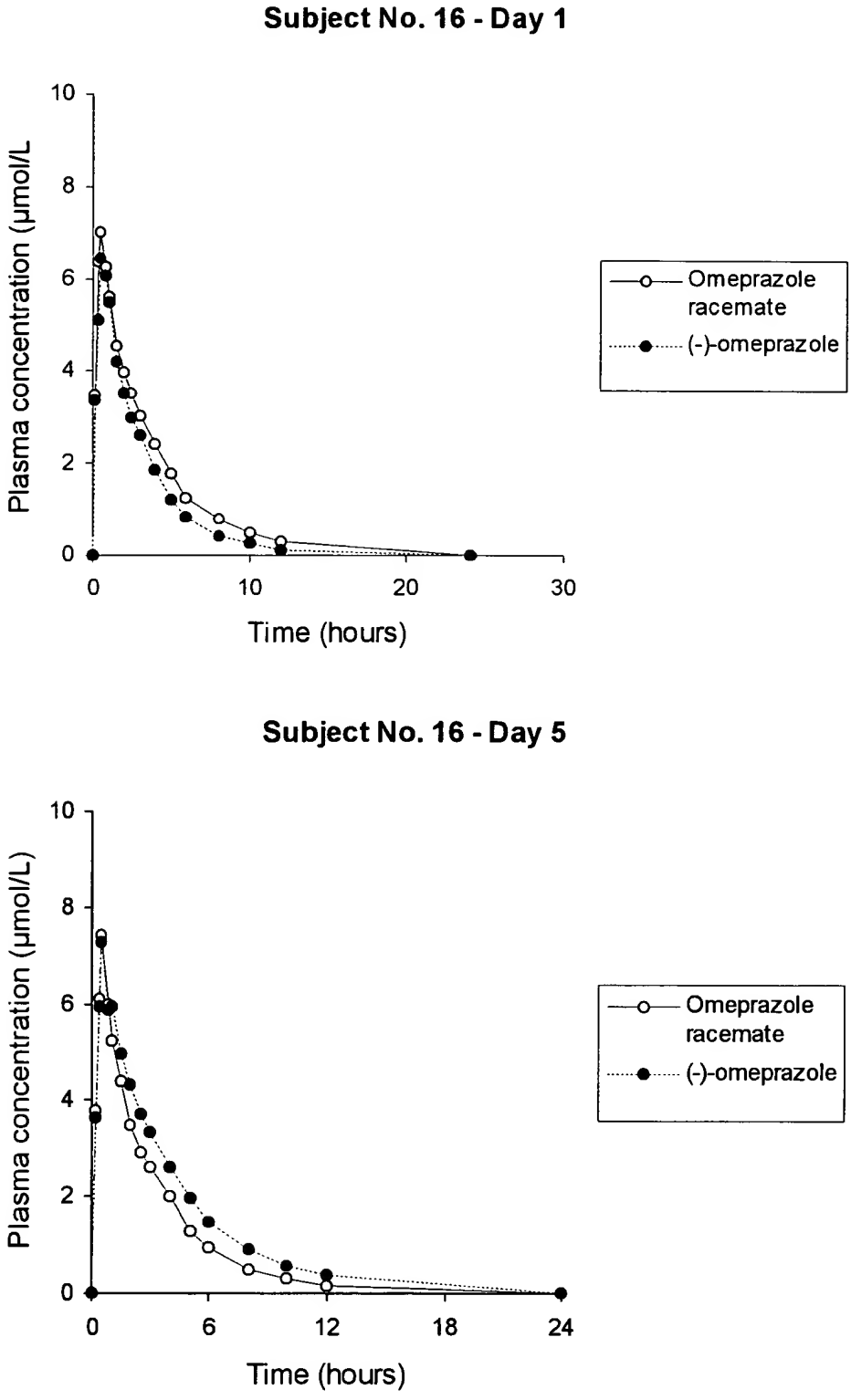


Figure 3. Plasma levels of (-)-omeprazole and omeprazole racemate after single (Day 1) and repeated (Day5) intravenous administration of the sodium salts of daily doses of 40 mg to a slow metabolizer (Subject No. 16).

CURRICULUM VITAE

Name:	Tommy Andersson.
Address:	113 Reveille Rd Wayne, PA 19087 USA
Date of birth:	March 28 1955.
Citizenship:	Swedish.
Education/academic degrees:	**Bsc** (1979); Chemistry, Biology, Physiology. Medical courses (1979-90); Pharmacology, Statistics, Clinical trial methodology, Pharmacokinetics & metabolism. **PhD** (1991); Clinical Pharmacology. **Associate Professor** (1998); Clinical Pharmacology
Present position:	1998-, Director, Clinical Pharmacology AstraZeneca, USA.
Previous employment:	**Marine Research Laboratory**, Lysekil, Sweden,1977-78, **Astra Hässle AB**, Mölndal, Sweden,1978-80, Dept of Pharmacology; 1981-92 Dept of Clinical Pharmacology (Pharmacokineticist) **Flinders Medical School**, Adelaide, Australia,1992-93, postdoc at Dept of Clinical Pharmacology under Profs Don Birkett and John Miners **Astra Hässle AB**, 1993-94, Dept of Clinical Pharmacology; 1994-96, Clinical Science; 1996-98, GI Management & Strategies (Project Team Leader & Scientific Adviser)
Membership of societies:	Swedish Pharmaceutical Society (section for pharmacokinetics and metabolism), ISSX (International Society for the Study of Xenobiotics), ASCPT (American Society for Clinical Pharmacology and Therapeutics), and EUFEPS (European Federation for Pharmaceutical Sciences)
Publications:	63 (including 25 abstracts, letters, and reviews) - mainly dealing with metabolism and drug-drug interactions of omeprazole and other proton pump inhibitors
Other information:	Specialist area; drug metabolism, drug-drug interactions, cytochrome P450, and pharmacokinetics in general

***Medical courses:** Pharmacology (Gothenburg University, 1979), Clinical trials (Clinical Research Services Limited, UK, 1982), Medical statistics (Gothenburg University, 1982), Clinical trials (Astra course, 1983), Pharmacokinetics (Rowland & Toozer, Germany, 1983), Biopharmaceutics and pharmacokinetics for candidates for the doctorate (Uppsala University, 1985), Clinical trial methodology from a statistical point of view (Astra course, 1985), Fundamental and applied drug metabolism (Swedish Pharmaceutical Society, 1989), Advanced methods in pharmacokinetics/pharmacodynamics (Rowland & Scheiner, University of California, San Francisco, 1990), Taking the project from IND to NDA with CCP och GCP (Astra course, 1991)

Other merits

Referee

Have been appointed "referee" for various manuscripts aimed for publication in international scientific journals, such as Xenobiotica, British Journal of Clinical Pharmacology, European Journal of Clinical Pharmacology, Therapeutic Drug Monitoring, och Fundamental & Clinical Pharmacology.

Internal and external presentations and seminars

"Pharmacokinetics of omeprazole", "Human pharmacology of omeprazole", "How much should gastric acid secretion be inhibited?", "Fundamental pharmacokinetics and metabolism", "Pharmacokinetics at liver disease", "Gastrointestinal circulation", "Mechanisms för different drug-drug interactions", "Drug metabolism with regard to cytochrome P450 - inhibition and induction", "Omeprazole and cytochrome P450 - interactions with other drugs", "Induction of CYP1A2 and potential carcinogenicity", "Pharmacokinetics and metabolism in children", "*In vitro* metabolism of omeprazole", "*In vitro* metabolism of diazepam", "Metabolism and drug-drug interactions with proton pump inhibitors"

Invited speaker to universities

"Pharmacokinetics of omeprazole with special reference to interaction studies" (Flinders Medical School, Adelaide, 1992), "*In vitro* metabolism of omeprazole" (Flinders Medical School, Adelaide, 1993), "*In vitro* metabolism of diazepam" (Flinders Medical School, Adelaide, 1993), "Omeprazole and cytochrome P450" (University of Michigan, Ann Arbor, 1994), "The metabolism of omeprazole and potential for interaction with other drugs" (Georgetown University, Washington, 1994), "Development of proton pump inhibitors beyond the year 2000" (Georgetown University, Washington, 1998).

Invited speaker to scientific meetings

Swedish Pharmaceutical Society meetings; "Primary and secondary metabolism of omeprazole in human liver microsomes", 1993 (see ref. 51), "Prediction of drug interactions *in vivo* from *in vitro* data. Omeprazole as an example", 1995 (see ref. 55).

Fifth European ISSX Meeting; "Primary and secondary metabolism of omeprazole in human liver microsomes", 1993 (see ref. 50).

12th International Symposium on Microsomes and Drug Oxidations, "Assessment of 2C19 activity", 1998

Papers

Original/full papers

1. Andersson T, Heath A, Mattsson H. Prenalterol as an antidote to massive doses of metoprolol - a cardiovascular study in the dog. Acta Med Scand 1982; Suppl 659: 71-88.

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4. Naesdal J, Andersson T, Bodemar G, Larsson R, Regårdh CG, Skånberg I, Walan A. Pharmacokinetics of ^{14}C omeprazole in patients with impaired renal function. Clin Pharmacol Ther 1986; 40: 344-351.

5. Lind T, Andersson T, Skånberg I, Olbe L. Biliary excretion of intravenous ^{14}C omeprazole in humans. Clin Pharmacol Ther 1987; 42: 504-508.

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7. Andersson T, Cederberg C, Edvardsson G, Heggelund A, Lundborg P. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. Clin Pharmacol Ther 1990; 47: 79-85.

8. Regårdh CG, Andersson T, Lagerström PO, Lundborg P, Skånberg I. The Pharmacokinetics of omeprazole in humans - a study of single intravenous and oral doses. Ther Drug Monit 1990; 12: 163-172.

9. Andersson T, Andrén K, Cederberg C, Lagerström PO, Lundborg P, Skånberg I. Pharmacokinetics and bioavailability of omeprazole after single and repeated oral administration in healthy subjects. Br J Clin Pharmacol 1990; 29: 557-563.

10. Andersson T, Andrén K, Cederberg C, Edvardsson G, Heggelund A, Lundborg P. Effect of omeprazole and cimetidine on plasma diazepam levels. Eur J Clin Pharmacol 1990; 39: 51-54.

11. Andersson T, Cederberg C, Regård CG, Skånberg I. Pharmacokinetics of various single intravenous and oral doses of omeprazole. Eur J Clin Pharmacol 1990; 39: 195-197.

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13. Andersson T, Lagerström P-O, Unge P. A study of the interaction between omeprazole and phenytoin in epileptic patients. Ther Drug Monit 1990; 12: 329-333.

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16. Andersson T, Cederberg C, Heggelund A, Lundborg P. The pharmacokinetics of single and repeated once-daily doses of 10, 20 and 40 mg omeprazole as enteric-coated granules. Drug Invest 1991; 3: 45-52.

17. Andersson T, Lundborg P, Regårdh CG. Lack of effect of omeprazole treatment on steady-state plasma levels of metoprolol. Eur J Clin Pharmacol 1991; 40: 61-65.

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